

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

REMARKS/ARGUMENTS

Status of the Claims

Claims 9, 10, 12-17, 19-25, 34-51, 57, and 58 were rejected. Claims 34-51 have been withdrawn from consideration as being drawn to non-elected inventions. To expedite prosecution, claims 1-8, 11, 18, 26-33, and 52-56 were previously canceled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application or to take other such appropriate action to seek protection of this canceled or withdrawn subject matter.

Claims 9, 10, 12, 17, 19, 20, 23, and 24 have been amended to clarify the invention or to correct minor grammatical or typographical errors. No new matter has been added by way of the claim amendments. Claims 9, 10, 12-17, 19-25, 34-51, 57, and 58 are now pending in the present application. Reexamination and reconsideration of the claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's rejections in the Final Office Action are addressed below in the order set forth therein.

The Objections to the Claims Should Be Withdrawn

Claims 10, 12, 17, 23, and 24 were objected to for minor informalities. The claims have been amended in accordance with the Examiner's recommendations. Therefore, the amendments to claims 10, 12, 17, 23, and 24 have obviated the objections.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 9, 10, 12-17, 19-25, 57, and 58 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for particularly pointing out and distinctly claiming the subject matter that Applicants regard as their invention. This rejection is traversed as to the pending claims.

The Examiner maintains that claims 9, 10, 13, 16, and 57 are indefinite because claims 9 contains steps directed to the manipulation of RNAs (i.e., steps (i) – (iii)) as well as steps directed to the manipulation of mRNAs. Applicants respectfully disagree with the Examiner's rejection. Applicants maintain that one of skill in the art would appreciate that claim 9(a) refers

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

to preparing a nucleic acid molecule that corresponds to the nucleotide sequence of the most 5' end of the mRNA of interest. It is this nucleic acid that is manipulated throughout the remainder of the claim. Claims 12, 14, 15, and 58 were similarly rejected as indefinite for recitation of this language. In view of the knowledge on the skilled artisan and the above remarks, Applicants respectfully request that the rejection of claims 9, 10, 12-16, 57, and 58 be withdrawn.

Claims 9, 12, 10, 13-17, 19-25, 57, and 58 were further rejected under 35 U.S.C. § 112, second paragraph, for lack of antecedent basis for the claim element “the 5’ end of an mRNA” at various points in these claims. As noted by the Examiner, sufficient antecedent basis exists for “the most 5’ end of the mRNA.” Accordingly, claims 9, 12, 10, 13-17, 19-25, 57, and 58 were amended in accordance with the Examiner’s suggestion, thereby by obviating the rejection.

Claims 17 and 19-25 were also rejected under 35 U.S.C. § 112, second paragraph, for recitation of the phrase “a second cDNA” when there is no mention of a first cDNA. Claim 17 has been amended to recite “a first strand cDNA” in step (ii), thereby obviating this rejection.

Claims 19-22 were rejected as indefinite because of the recitation of “the second-strand cDNA” when there is no mention of a first cDNA. Claim 19 has been amended to delete the word “second,” thereby obviating this rejection.

Claims 20-22 were further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for lack of antecedent basis for the claim element “the recovering step.” Claim 20 has been amended to recite “a collecting step,” thereby eliminating any antecedent basis issue.

The Rejection of the Claims Under 35 U.S.C. § 102 Should be Withdrawn

Claims 17, 19-21, and 23-25 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2003/0113737 (hereinafter “the ‘737 publication”). This rejection is respectfully traversed as to the pending claims.

The ‘737 publication discloses a method similar to the process of “molecular indexing,” although the approach of the method of the cited reference targets the isolation of single-stranded tags for analysis. Such single-stranded tags are isolated by means of one or two restriction endonucleases, one of which preferably nicks double-stranded DNA, wherein the nicked DNA strand will yield the single-stranded tag. The location and length of the singled-stranded tag is

determined by the position of the recognition site(s) and the type of restriction endonucleases used.

Applicants reiterate that the methods of the '737 publication require single-stranded DNA for further manipulation and analysis. These sites can be randomly distributed within the DNA, which implies that the site will likely be away from the sequence corresponding to the transcription start site. In addition, the location of the single-stranded tag is determined by the position of the recognition site and the type of restriction endonuclease used, whereas in the method of the present invention the 3' end of the tags is determined distance between the recognition site of the endonuclease and the site where the enzyme cleaves the double-stranded DNA.

Claim 17 has been amended solely for the purposes of expediting prosecution and now recites "a resulting double-stranded DNA fragment." Accordingly, the purpose of the present invention is to obtain a double-stranded tag. In contrast to the presently claimed methods, the '737 publication describes a process for obtaining a single-stranded polynucleotide tag. See, for example, lines 2-3 of the Abstract and paragraph [0025] of the '737 publication. Single-stranded polynucleotide tags without any linker sequence and any complementary strand reduce the complexities associated with the analysis of expressed molecules in a biological sample. *Id.* The resulting single-stranded polynucleotide tags of the cited reference are used for hybridization, such as LCR, Northern blots, and PCR, not for sequencing the tag itself. For hybridization of the tags as described in the '737 publication, an extra sequence such as a linker sequence in the tag and the complementary strand should not be included because the problems associated with the analysis of expressed molecules increases. If such extra sequences are included in the tag, non-specific and undesirable background noise will increase when the hybridization is carried out, as in the cited reference.

Again, in contrast to the '737 publication, the purpose of the instant invention is primarily the sequencing of the resulting tags. As shown in the figures of the present application, the tags are double-stranded and are attached to linker sequences. Double-stranded DNA tags having linker sequences and complementary strands, as presently claimed, are not suitable for use in the methods of the cited reference. The double-stranded DNA tags of the present invention have a

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

linker sequence that is necessary to sequence the tags. In order to sequence the tags, extra sequences (i.e., a linker sequence and the complementary strand) must be included.

Furthermore, the nicking endonuclease is essential in the method of the '737 publication, whereas the nicking endonuclease is not required in the claimed methods. The Examiner asserts on page 7 of the present Final Office Action that the DNA fragment produced in the cited reference by digestion with the nicking enzyme and the TypeIIS endonuclease includes a region corresponding to the 5' terminus of the mRNA. The Applicants respectfully disagree and again point out that the methods of the invention do not require any nicking endonuclease. In the '737 publication, in order to obtain the single-stranded tag, a nicking endonuclease must be used. See the Abstract and paragraph [0025]. A nicking endonuclease is not required in the present invention at all because the amended claims recite a method for preparing a double-stranded DNA fragment and "collecting a resulting double-stranded fragment" (see step (d)).

Applicants also maintain that the DNA fragment corresponding to the most 5' end cannot be obtained by the method set forth in the '737 publication, in contrast to the claimed methods. The Examiner, however, asserts on page 7 of the present Final Office Action that the cited reference does in fact disclose a method for isolating a DNA fragment corresponding to the 5' terminus of an mRNA molecule. The Applicants respectfully disagree.

The method of the '737 publication does not produce fragments corresponding to the most 5' end of an mRNA molecule, as recited in the instant claims. The Examples of the cited reference demonstrate this point. See, for example, paragraphs [0791] to [0793]. In contrast, the presently claimed methods result in a DNA fragment that contains the most 5' end of an mRNA molecule. Therefore, the rejection of claims 17, 19-21, and 23-25 should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claim 22 was rejected under 35 U.S.C. § 103(a) as being unpatentable over the '737 publication in view of U.S. Patent No. 5,484,701 (hereinafter "the '701 patent). This rejection is respectfully traversed.

The teachings of the '737 publication are described above. The '701 patent is drawn to a method for isolating primer extension products and generating them in a form appropriate for

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

electrophoresis by utilizing the biotin-avidin/streptavidin system or a digoxigenin-digoxigenin antibody capture system. In particular, the '701 patent describes a method for enrichment or purification of primer extension products by making use of a biotinylated primer, enriching the biotinylated reaction product on a solid support having an immobilized biotin-binding protein attached to it, and removing the biotinylated reaction product from the solid support by formamide treatment. Enriched reaction products are preferably analyzed by gel electrophoresis. The use of a biotin group in the present invention is unrelated to the method of the '701 patent, specifically because the '701 patent neither teaches the purification product obtained from a primer extension product nor does the reference teach the release of the reaction product by the use of PCR, as recited in the present claims. The Examiner asserts that the skilled artisan would have been motivated to combine the teachings of the '737 publication and the '701 patent to arrive at the method of claim 22. Applicants respectfully disagree with the Examiner's conclusions.

A *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obviousness requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In fact, the Examiner herself has acknowledged that the '737 publication "does not teach [the recited element of claim 17] that the first strand cDNA is ligated to a double-stranded linker, which is then used to prime second strand cDNA synthesis." See page 22, Office Action mailed March 4, 2008. This deficiency is not cured by the teachings of the '701 patent. Here, the cited references do not disclose, either explicitly or implicitly, the recited claim element of ligation of the first strand cDNA to a double-stranded linker, which is then used to prime second strand cDNA synthesis. As mentioned above in detail, the present methods differ from those of the '737 publication in that (1) the purpose of the present method is to obtain a double-stranded DNA tag rather than a single-stranded DNA tag that lacks both a linker and a complementary strand; (2) a nicking endonuclease is not required in the claimed methods; and (3) a fragment

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

corresponding to the most 5' end can be obtained by the present methods. Thus, the disclosures of the cited references simply cannot be combined to arrive at the claimed method.

Furthermore, although in the present case the references simply cannot be combined to produce the claimed invention, the Examiner has also merely provided broad conclusory statements and has failed to identify a sufficient reason that one of skill in the art would have been motivated to combine the cited references and would have concluded that the method of claim 22 is obvious in view of this combination. Accordingly, in view of the above remarks, Applicants respectfully request that the obviousness rejection of claim 22 be withdrawn.

Claims 9, 10, 12, 14-16, and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the (“‘937 patent”) in further view of Carninci *et al.* (1996) *Genomics* 37:327-336. As indicated in the listing of claims, step (b) of claims 9 and 12 has been amended to recite “at least one linker to the end corresponding to the most 5' end of the mRNA.” This rejection is respectfully traversed as to the pending claims.

The ‘937 patent discloses a method for Serial Analysis of Gene Expression (SAGE) that permits numerous transcripts to be analyzed in order to determine the overall gene expression pattern in various cell types. As discussed in paragraphs [0005] through [0010] of the present application, the 3' ends of mRNA molecules, rather than the 5' ends recited in the claims, are collected with high prevalence via the SAGE method disclosed in the ‘937 patent. Further evidence in support of this statement is provided in Velculescu *et al.* (1995) *Science* 270: 484-487. See, particularly, pages 484, right-hand column; page 486, left-hand column; and Table 2. A copy of this reference was previously submitted for the Examiner’s consideration. In contrast to the techniques disclosed in the ‘937 patent, the present method claims recite the collection of the DNA fragments corresponding to the most 5' end of mRNAs. The collection of such 5' end fragments is particularly advantageous for such applications as promoter mapping and analysis, which simply cannot be accomplished using molecules corresponding to the 3' ends of mRNAs. Applicants further note that the method disclosed in the cited reference cannot be used to obtain the most 5' end of an RNA having a cap structure or any cDNA derived therefrom.

The ‘937 patent only teaches the *possibility* of the isolation of sequences in relation to the most 5' recognition site of an endonuclease, which is unlikely to include the most 5' sequence of an mRNA or any cDNA derived therefrom. The cited reference does not teach a specific method for obtaining the most 5' sequence from a pool of digested nucleic acid fragments. As discussed herein above, the 5' sequences obtained by the method of the ‘937 patent are not equivalent to the most 5' end of mRNAs that are obtained via the claimed methods. The “5' ends” that are obtained according to the method of the ‘937 patent may be 100 basepairs or more from the transcription start site. Applicants reiterate the importance of obtaining the most 5' end of an mRNA, as this sequence contains transcription start site and related promoter regions. Such sequences permit analysis of transcription start site and promoter identification in genomic sequences.

Applicants further note that the method disclosed in the ‘937 patent requires two digestion steps utilizing two endonucleases. The first endonuclease cleaves the cDNA at a defined position in the cDNA, thereby producing the defined sequence tags. That is, the first digestion marks the location of the DNA fragment that is isolated in a second digestion step. The first digestion step makes use of an internal recognition sit within the cDNA, and the location of such recognition site depends on each mRNA molecule. Since the method of the cited reference requires an internal recognition site, it cannot isolate the most 5' nucleotides of an mRNA or cDNA molecule. In contrast to the method of the ‘937 patent, the instant method uses only one endonuclease digestion step, and the recognition site for the endonuclease is introduced by a linker placed adjacent to the 5' end of an mRNA or a cDNA derived therefrom. Indeed, the strategy disclosed in the ‘937 patent is based on the above cDNA cleavage, which would cleave elsewhere *inside* the transcripts. Therefore, the “5' end” of a DNA fragment obtained by the method of the ‘937 patent does not correspond to the mRNA/RNA transcription start site

The Carninci *et al.* reference is drawn a method for constructing high-content full-length cDNA libraries based on chemical introduction of a biotin group into the cap structure of a eukaryotic mRNA molecule. This reference does not teach or suggest utilizing any 5' cap structure in a method for preparing DNA *fragments* corresponding to a nucleotide sequence of a 5' end region of an mRNA, as recited in all of the rejected claims. The Examiner maintains that

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

it would have been obvious to one of skill in the art to combine the disclosures of the ‘937 patent and the Carninci *et al.* reference to produce the methods of claims 9, 10, 12, 14-16, and 58. Applicants respectfully disagree with the Examiner’s conclusions.

Establishing a *prima facie* case of obviousness requires assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), which provides the framework for applying the statutory language of § 103. Under the “Graham Factors,” the Examiner is required to:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Although Applicants do not concede that a *prima facie* case of obviousness has been established for claims 9, 10, 12, 14-16, and 58, secondary considerations of the advantageous properties of the claimed methods (e.g., the collection of molecules corresponding to 5' mRNA ends by the practice of the present methods versus the high prevalence of 3' mRNA ends collected via the SAGE technique disclosed in the ‘937 patent, provide additional support for the nonobviousness of the pending claims (see, for example, paragraphs [0005] through [0010] of the present application). See *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) and *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). As discussed above, the collection of fragments corresponding to the 5' end of an mRNA molecule rather than the 3' end permits, for example, promoter mapping and analysis. The method of the ‘937 patent results primarily in the collection of 3' ends of mRNA molecules and does not any provide information regarding the 5' end of transcripts or allow for promoter analysis. Applicants respectfully remind the Examiner that the secondary consideration of superior and advantageous results obtained with an invention provides objective indicia of nonobviousness. See, for example, *In re Mayne*, 104F.3d 1339, 1342, 41USPQ2d 1451, 1454 (Fed. Cir. 1997) and *In re Woodruff*, 919F.2d 1575, 1578, 16 USPQ2d 1934,1936-37 (Fed. Cir. 1990). Such “secondary considerations” as those noted above further support the conclusion that the rejected claims are not obvious.

Applicants further note that combining the method of the ‘937 patent with the oligo-capping and cap trapper methods of the Carninci *et al.* reference leads to the isolation of DNA

fragments that are clearly distinct from the most 5' end obtained by the present method, both in their sequence and their location within the mRNA or cDNA derived therefrom. Thus, it is not obvious to combine the cited references.

According to the method of the '937 patent, the linker is attached to the nucleotide sequence tag on the opposite side to which the linker of the present methods is attached. The Examiner asserts on page 16 of the instant Final Office Action that application of the methods of the Carninci *et al.* reference regarding capturing the 5' mRNA cap would result in a method wherein an mRNA molecule is captured via its 5' terminus onto a solid support, cleaved with an anchoring enzyme, and ligated with a linker at the end cleaved by the first enzyme. As recited in amended claims 9 and 12, the linker is attached to the most 5' end of the mRNA in the nucleic acid. The linker of the '937 patent, however, is not attached to the most 5' or 3' end. See, for example, column 5, lines 39-41 of the cited reference. Thus, the linker is attached to the cleavage site of the anchoring enzyme (i.e., the restriction endonuclease), which is not the most 5' or 3' end.

Furthermore, the DNA fragment corresponding to the most 5' end cannot be obtained by the combination of the cited references. The Examiner asserts on page 16 of the present Final Office Action that application of the teachings of the Carninci *et al.* reference to the methods of the '937 patent results in the isolation of a nucleic acid corresponding to the 5' terminus of an mRNA molecule. The Applicants respectfully disagree with the Examiner's conclusions. As explained above, in accordance with the methods of the '937 patent, the linker is attached to the nucleotide sequence tag on the side opposite to the most 5' end of an mRNA molecule. In other words, the linker is attached to the nucleotide sequence tag via the cleavage site of the anchoring enzyme. The sequence corresponding to the most 5' end contains a promoter with a high GT content. According to the method of the '937 patent, when an anchoring enzyme recognizes a GC-rich sequence, the resulting nucleotide sequence, after digestion with the anchoring enzyme, is a short fragment. In contrast, when an anchoring enzyme recognizes an AT-rich sequence, the resulting nucleotide sequence, after digestions with the anchoring enzyme, is a long fragment.

After the defined nucleotide sequence is digested with the anchoring enzyme, if the isolated nucleotide sequence tags are so short that the cleavage site of the tagging enzyme, which

is distinct from the recognition site, cannot be included in the isolated nucleotide sequence tags attached to linkers, and the tagging enzyme cannot cleave the nucleotide sequence tags. For example, when BsmFI, which cleaves at a site 10-14 nucleotides away from the recognition site, is used as a tagging enzyme, an isolated nucleotide sequence tag with ten or fewer nucleotides cannot be cleaved with BsmFI. After the double-stranded cDNA is digested with the anchoring enzyme, if the isolated nucleotide sequence tags are too long, however, the tagging enzyme cleaves at a site away from the end corresponding to the most 5' or 3' end. Therefore, in either of these situations, the most 5' or 3' end of an mRNA molecule cannot be obtained by the combination of the teachings of the Carninci *et al.* reference and the '937 patent.

The Examiner further asserts on page 17 of the present Final Office Action that an ordinary artisan would have been motivated to attach a biotin molecule to the mRNA template, as suggested by the Carninci *et al.* reference, prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, thereby improving the ability of generating 5' end-specific tags using the method of the '937 patent. The Applicants respectfully disagree with the Examiner's conclusions.

Specifically, according to the Carninci *et al.* reference, the first strand cDNA, after treatment with RNaseH and mild alkaline RNA hydrolysis, does not have a biotin group because the biotin group is present on the cap structure of the mRNA. See Figure 1C of the Carninci *et al.* reference. Then, using the resulting full-length first strand cDNA as a template, the second strand cDNA is synthesized. According to the method of the '937 patent, however, the resulting double stranded cDNA is digested with the anchoring enzyme. If the methods of the two cited references are combined, the nucleotide sequence tag corresponding to the most 5' end of an mRNA cannot be captured because the double stranded cDNA does not have a biotin group.

Moreover, although the U.S. Supreme Court declined to permit a "rigid" application of the teaching-suggestion-motivation to combine (TSM) test to obviousness determinations, the Court did hold that the presence or absence of a teaching, suggestion, or motivation to combine the cited references provides a "helpful insight" regarding the obviousness of an invention. *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1389 (U.S. 2007). The Supreme Court went on to acknowledge the importance in making obvious determinations of identifying "a reason that

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does.” *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007; citing *KSR Int’l Co. v. Teleflex, Inc.*).

In the instant case, the Examiner has merely pieced together the claimed invention by citing two unrelated references, namely the first drawn to a method for analysis of transcripts in order to determine the overall pattern of gene expression (i.e., the ‘937 patent) and the second directed to full-length cDNA cloning (i.e., Carninci *et al.*). Given the lack of evidence of a reason to combine the references, it appears that the Examiner has engaged in impermissible “hindsight reconstruction” in formulating the present rejection. See *In re Fine*, 5 USPQ2d 1071, 1075 (Fed. Cir. 1988) (holding that “[o]ne cannot use hindsight reconstruction to pick and choose among disclosures in the prior art to deprecate the claimed invention”) and *Graham v. John Deere Co.*, *supra* (stating the importance of guarding against “slipping into hindsight and...resisting [the] temptation to read into the prior art the teachings of the invention in issue”). Therefore, in establishing obviousness, it is improper “to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Accordingly, the lack of a *reason* to combine the cited references to arrive at the claimed methods provides additional evidence that claims 9, 10, 12, 14-16, and 58 are not obvious.

In view of the above remarks, the secondary considerations of nonobviousness, particularly the superior and advantageous results obtained by the practice of the claimed methods (e.g., the collection of DNA fragments corresponding to the 5' end of an mRNA), and the lack of a reason to combine the cited references, Applicants respectfully request that the rejection of claims 9, 10, 12, 14-16, and 58 under 35 U.S.C. § 103(a) be withdrawn.

Claims 13 and 57 were again rejected under 35 U.S.C. § 103(a) as being unpatentable over the ‘937 patent in further view of Carninci *et al.* (1996) *Genomics* 37:327-336, Edery *et al.* (1995) *Mol. Cell. Biol.* 15(6):3363-3371, and Das *et al.* (2001) *Physiol. Genomics* 6:57-80. This rejection is respectfully traversed.

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

The teachings of the '937 patent and the Carninci *et al.* reference are described above. The Edery *et al.* reference discloses a method for isolating full-length cDNAs based on an mRNA cap retention procedure. The Das *et al.* reference is simply a review article that analyzes and compares a variety of techniques for isolating full-length cDNAs. Neither Edery *et al.* nor Das *et al.*, however, teach or suggest the preparation and collection of DNA fragments corresponding to the most 5' end of mRNAs. The Examiner concludes that one of skill in the art would have motivated to combine the cited references to arrive at the methods of claims 13 and 57. Applicants respectfully disagree with the Examiner's assertions.

Applicants reiterate that secondary considerations such as superior and advantageous properties support the nonobviousness of claims 13 and 57. In particular, the methods of the rejected claims result in the collection of DNA fragments corresponding to the 5' ends of mRNAs, thereby permitting, for example, promoter mapping and analysis that cannot be achieved with samples comprising the 3' ends of transcripts in high prevalence, such as those obtained by the methods of the '937 patent. Moreover, Applicants respectfully submit that the Examiner has merely "pieced together" four unrelated references to allegedly produce the claimed methods without providing a sufficient "reason" that one of skill in the art would have been motivated to combine these references. Such "hindsight reconstruction" is impermissible.

As mentioned above in greater detail, the '937 patent and the Carninci *et al.* reference cannot be combined to arrive at the claimed methods. Thus, even though Edery *et al.* and Das *et al.* references may teach a cap-binding protein, the cited references still cannot be combined to produce the methods of the invention.

In view of the above remarks, the secondary considerations of nonobviousness, specifically the superior and advantageous results obtained by the practice of the claimed methods (e.g., collection of DNA fragments corresponding to the 5' end of an mRNA molecule), and the lack of a reason to combine the four cited references, Applicants respectfully request that the rejection of claims 13 and 57 under 35 U.S.C. § 103(a) be withdrawn.

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
Reply to Office action of Februray 19, 2009

CONCLUSION

The Examiner is respectfully requested to withdraw the rejections of the claims. In any event, the Examiner is respectfully requested to consider the above remarks (and previously submitted evidence) and to enter them into the record for the purposes of further prosecution.

Pursuant to 37 C.F.R. § 1.116 and MPEP § 714.12, any argument that will place the application in condition for allowance may be entered after final rejection. The above arguments and references were not presented earlier as Applicants earnestly believe that the specification and claims as originally filed are patentable. Applicants trust that the above remarks place the claims in condition for allowance.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/michelle l. cunningham/

Michelle L. Cunningham
Registration No. 51,072

Appl. No.: 10/517,544
Amdt. dated June 19, 2009
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Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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